CASE REPORT
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Naloxone-Induced Pulmonary Edema

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We present the case of a 68-year-old woman with acute pulmonary edema secondary to the administration of naloxone to reverse an inadvertent narcotic overdose. The patient presented following a 12-hour history of increasingly bizarre behavior and confusion. A total IV dose of 1.6 mg naloxone was administered in an attempt to reverse the suspected overconsumption of a codeine-containing cough suppressant. She immediately became agitated, tachycardic, and diaphoretic; a clinical diagnosis of acute pulmonary edema was made. Following treatment with furosemide, nitroglycerin, and morphine sulfate, the patient recovered completely without further incident. Although naloxone is thought to be a safe drug with few complications, it should not be used indiscriminantly, and the smallest doses necessary to elicit the desired response should be used. [Schwartz JA, Koenigsberg MD: Naloxone-induced pulmonary edema. Ann Emerg Med November 1987;16:1294-1296.]

INTRODUCTION

Naloxone is an opiate antagonist without intrinsic agonist activity used for the reversal of narcotic-induced respiratory depression and in the diagnosis of suspected acute opiate overdosage. While being structurally similar to oxymorphine, it is essentially a pure narcotic antagonist that counteracts the effects of narcotics, including respiratory depression, coma, analgesia, pupillary constriction, seizures, and cardiovascular and gastrointestinal effects. Naloxone may precipitate withdrawal symptoms in individuals with physical narcotic dependency. In general, naloxone is widely accepted to be a benign drug with few adverse side effects or contraindications.

We present a case of acute pulmonary edema after naloxone administration, an unusual adverse reaction previously unreported in the emergency medicine literature.

CASE REPORT

A 68-year-old woman was brought to the emergency department because of increasing confusion and hemoptysis. Her daughter stated that the patient had been coughing up small amounts of bright red blood-tinged sputum for two days. In addition, the patient's behavior had become increasingly bizarre, with increased confusion during the past 12 hours. Her medical history included tuberculosis treated with a right partial pneumonectomy 20 years earlier, hypertension, and multiple prior episodes of hemoptysis that were associated with numerous previous hospitalizations. Current medications included furosemide, a potassium supplement, and a codeine-containing cough syrup for a chronic cough. The patient's daughter also expressed some concern that her mother might be addicted to the codeine-containing cough syrup because she had been seen using it frequently.

Physical examination revealed an elderly woman in no acute distress sitting in an upright position. Blood pressure was 112/64 mm Hg; pulse, 96; respirations, 20; and temperature, 36.9 C orally. Pupils were pinpoint, equal, and reactive bilaterally. Peripheral cyanosis was noted in a bluish discoloration of the patient's lips and nail beds. Breath sounds revealed scattered expiratory rhonchi with few inspiratory dry rhonchi at the left lung base. Cardiac examination revealed a regular rate and rhythm with normal heart sounds and no evidence of murmur, gallop, jugular venous distension, or

peripheral edema.

Although the patient was awake and alert, she was unable to answer questions appropriately and appeared confused when questioned. Additional testing involving the cranial nerves; sensory, motor, and cerebellar systems; and deep-tendon reflexes were all grossly intact without focal neurologic deficits.

Following the establishment of a peripheral IV line of D5/.45 normal saline at 40 mL/hr, arterial blood gases were obtained on room air, and the patient subsequently was begun on supplemental oxygen at 2 L/min through a nasal cannula. In an attempt to reverse the suspected narcotic overdosage from an inadvertent over-consumption of codeine contained in the self-administered cough suppressant, naloxone was administered in total dose of 1.6 mg (four 0.4-mg preload ampules) IV over three minutes.

Following completion of naloxone administration, the patient immediately and dramatically became agitated, was tachycardic with a pulse of 124, and diaphoretic, and complained of severe dyspnea. Auscultation revealed inspiratory and expiratory wet rales throughout all lung fields. The clinical diagnosis of acute pulmonary edema was made. Within ten minutes following the administration of furosemide 40 mg IV, nitroglycerin 0.04 mg sublingually, and morphine sulfate 2 mg IV, resolution of all subjective and objective signs of acute pulmonary edema occurred. Repeat physical examination at this time revealed a tremulous, slightly anxious patient with blood pressure of 140/50 mm Hg, pulse of 100, and respirations of 24. The patient's pupils were dilated bilaterally. The skin and mucosal membranes were now pink, and the diaphoresis had resolved. Cardiopulmonary examination revealed scattered wheezes in the upper lung fields and dry rhonchi at the bases bilaterally. The remainder of the physical examination remained unchanged with the exception of a pulse of 112.

Following resolution of the patient's condition, the initial ABG obtained on room air became available. The initial blood gas revealed pH, 7.33; pCO_2, 72.4 mm Hg; pO_2, 50.6 mm Hg; and HCO_3, 37.1 m/EqL. Supplemental oxygen therapy was changed to 24% venti-mask at this time. Chest radiograph revealed an old right upper pneumonectomy with a possible superimposed active infiltrate; no signs of acute pulmonary edema or congestive heart failure were noted. Additional laboratory tests, including CBC, PT, PTT, electrolytes, BUN, creatinine, and glucose, were normal.

Following the patient's admission to the hospital, a codeine level of 1,188 mg/mL was found. While no additional episodes of pulmonary edema were noted during hospitalization, further evidence of acute narcotic withdrawal, including yawning, lacrimation, piloerection, tremors, and insomnia were seen. The patient was discharged from the hospital two days later, with no complications.

DISCUSSION

In recent years reports have appeared linking naloxone administration to adverse cardiovascular effects in patients. Tanaka[1] first reported a case of severe hypertension and atrial tachycardia following administration of 0.4 mg naloxone to antagonize the respiratory depressant effects of morphine-nitrous oxide anesthesia in a 51-year-old man with a history of hypertension, hyperlipidemia, and diabetes mellitus. Michaelis et al[2] observed ventricular fibrillation and tachycardia in two patients undergoing open heart surgery following 0.1 to 0.4 mg naloxone administered to reverse morphine anesthesia. Flacke et al[3] were the first to report the sudden onset of acute pulmonary edema in a patient undergoing coronary bypass surgery following "high-dose" (0.4 mg) naloxone administration.

While these adverse effects were noted in patients with pre-existing cardiac disease, recently reported cases include young, previously healthy individuals. In 1980, Andree[4] reported the death of two healthy women following narcotic reversal with naloxone leading to cardiac arrest. Taff[5] and Prough et al[6] reported acute pulmonary edema following low-dose (0.04 to 0.10 mg) naloxone administration used to reverse anesthesia in previously healthy young adults without underlying cardiovascular disease who were undergoing elective surgery.

Most authors attribute the adverse cardiovascular effects of naloxone to the reversal of narcotic analgesia and the subsequent central release of endogenous catecholamines leading to a massive sympathetic response.[1,3,5-7] Others have suggested the precipitation of noncardiogenic pulmonary edema as similar to neurogenic pulmonary edema, a type of adult respiratory distress syndrome that may occur in the absence of underlying cardiac pulmonary disease.[6] In addition, a possible unknown effect of naloxone on peripheral opioid receptors outside the central nervous system or drug-drug interactions of an unknown variety have been conjectured.[7] The reaction does not appear to be allergic in nature, as the usual signs and symptoms of an anaphylactic reaction were not present in any of the reports.

The sudden and unexpected presentation of acute pulmonary edema immediately following the administration of IV naloxone in our patient reiterates the findings previously lim-

ited to the post-surgical and anesthesia literature. Our patient's confusion, lethargy, pupillary constriction, and cyanosis were thought to be secondary to inadvertent over-administration of a codeine- and alcohol-based elixir used as an antitussive. Naloxone was used to reverse the acute mental obtundation present. The acute pulmonary edema that developed immediately following naloxone administration was reversed quickly and never recurred during the patient's remaining hospitalization.

Because vital signs were obtained neither immediately following naloxone administration nor during the precipitious occurrence of acute pulmonary edema, we are unable to speculate whether the cause of the pulmonary edema was due to a direct effect of the naloxone or to an indirect effect secondary to an outpouring of endogenous catecholamines, yielding a massive sympathetic response leading to an acute hypertensive episode as the precipitating factor.

SUMMARY

Due to the immediate temporal relationship between the precipitous development of acute pulmonary edema and the administration of naloxone, we believe that the observed events in this patient were related to naloxone administration. This concept is supported by the previously reported similar occurrences of precipitation of acute pulmonary edema following naloxone administration.[3-7] It is plausible that had we begun with 0.4 to 0.8 mg naloxone over five minutes rather than 1.6 mg over three minutes, our patient might have experienced a controlled, partial reversal of the mental obtundation associated with codeine intoxication without experiencing the observed morbidity and possible mortality of pulmonary edema.

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